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https://doi.org/10.5281/zenodo.1239010 **Case Report**

The Effect of Intravitreal Injection of Anti-VEGF on Macular Edema and Visual Acuity, after Central Retinal Vein Occlusion

Healthcare

Keywords: CRVO, macular edema, coroidal neovascularisation, visual acuity, anti-VEGF treatment.

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Abstract

Central retinal vein occlusion (CRVO) is a common retinal vascular disorder which affect the patient visual ability. Visual prognosis depends on the type of retinal vein occlusion, that can be ischemic or non-ichemic, its severity, degree of retinal ischemia or macular edema and development of complications. The two most frequent complications of CRVO are persistent macular edema and neovascularization. One of the best and effective treatment for macular edema and neovascularisation seems to be intra vitreal anti-VEGF. Case report: We report 3 cases of CRVO with macular edema, treated with 3 intavitreal aflibercept (EYLEA) in 3 months. The Visual acuity (VA) improved on all 3 cases after each injection. This article aims to review the effect of anti-VEGF drugs in macular edema and improving vision in patients with CRVO.

Introduction

Retinal vein occlusion (RVO) is a common cause of vision loss in older individuals, and the second most common retinal vascular disease after diabetic retinopathy. CRVO is divided into the categories of perfused (nonischemic) and nonperfused (ischemic), each of which has implications for prognosis and treatment. On initial presentation, it may be difficult to classify a given patient into either category, since CRVO may change with time. Nonischemic CRVO is the milder form of the disease. It may present with good vision, few retinal hemorrhages and cotton-wool spots, no relative afferent pupillary defect, and good perfusion to the retina (figure nr. 1).

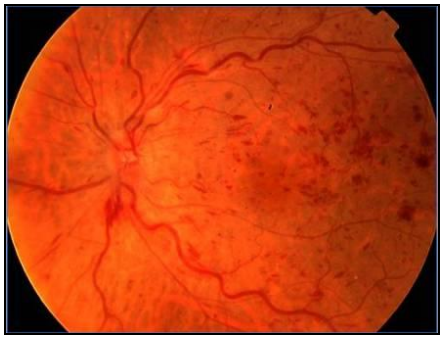

Figure 1.

Nonischemic CRVO may resolve fully with good visual outcome or may progress to the ischemic type. Ischemic CRVO is the severe form of the disease. CRVO may present initially as the ischemic type, or it may progress from nonischemic. Usually, ischemic CRVO presents with severe visual loss, extensive retinal hemorrhages and cotton-wool spots, presence of relative afferent pupillary defect, poor perfusion to retina, and presence of severe electroretinographic

changes (Figure nr. 2). In addition, patients may end up with neovascular glaucoma and a painful blind eye.

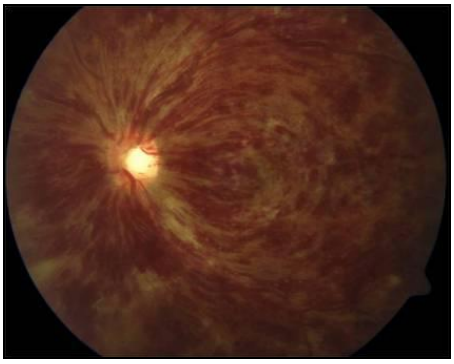

Figure 2.

The exact pathogenesis of the thrombotic occlusion of the central retinal vein is not known. Arteriosclerotic changes in the central retinal artery transform the artery into a rigid structure and impinge upon the pliable central retinal vein, causing hemodynamic disturbances, endothelial damage, and thrombus formation. Thrombotic occlusion of the central retinal vein can occur as a result of various pathologic insults, including compression of the vein (mechanical pressure due to structural changes in lamina cribrosa, eg, glaucomatous cupping, inflammatory swelling in optic nerve, orbital disorders); hemodynamic disturbances (associated with hyperdynamic or sluggish circulation); vessel wall changes (eg, vasculitis); and changes in the blood (eg, deficiency of thrombolytic factors, increase in clotting factors). It has been postulated that ischemic damage to the retina stimulates increased production of vascular endothelial growth factor (VEGF) in the vitreous cavity. Increased levels of VEGF stimulate neovascularization of the posterior and anterior segment (responsible for secondary complications due to CRVO). Also, it has been shown that VEGF causes capillary leakage leading to macular edema (which is the leading cause of visual loss in both ischemic CRVO and nonischemic CRVO). Approximately 81% of the patients with CRVO are of the non-ischemic, and only 19% are of the ischemic type.

Risk factors in CRVO:

Hypertension
Diabetes mellitus
Cardiovascular disorders
Bleeding or clotting disorders,polycythemia vera, lymphoma, leukemia
Alcohol consumption
Amount of physical activity
Vasculitis, Syphilis, sarcoidosis
Autoimmune disorders,Systemic lupus erythematosus
Use of oral contraceptives
Closed-head trauma
Primary open-angle glaucoma or angle-closure glaucoma

Ocular symptoms at initial presentation are as follows:

Asymptomatic
Decreased vision

Visual loss can be sudden or gradual, over a period of days to weeks. Visual loss ranges from mild to severe. Patients can present with transient obscurations of vision initially, later progressing to constant visual loss.

Photophobia
Painful blind eye
Redness of eyes

Ocular symptoms in later stages are as follows:

Decrease of vision
Pain in the eye
Discomfort
Redness
Watering

Clinical Presentation & Diagnosis

CRVO is classically characterized by optic disc swelling, increased venous dilatation and tortuosity, widespread deep and superficial hemorrhages, cotton wool spots, retinal edema, and capillary nonperfusion. A number of clinical and fluorescein angiographic features can help to distinguish between ischemic and non-ischemic CRVO. Ischemic CRVO is more severe, and is associated with profound visual loss (visual acuity worse than 20/200), severe clinical signs and a marked afferent pupillary defect. However, during the early acute phase of CRVO, such differentiation can be less distinct and a combination of functional tests may be required to achieve a more accurate diagnosis to aid the management plan. Iris neovascularization develops in approximately 35% of eyes with a risk of neovascular glaucoma, unless they are treated vigorously with panretinal photocoagulation. As a general rule, this risk of iris neovascularization is higher if the area of retinal ischemia (retinal nonperfusion as determined by fluorescein angiogram) is >10 disc diameters.

Patients with central retinal vein occlusion (CRVO) should undergo a complete eye examination, including visual acuity, pupillary reactions, slit lamp examination of the anterior and posterior segments, undilated examination of the iris, gonioscopy, fundus examination with indirect ophthalmoscope, and fundus contact lens.

Laboratory test (all patients)

Blood pressure, Erythrocyte sedimentation rate (ESR), Full blood count (FBC), Random blood glucose, Random total and HDL cholesterol, Plasma protein electrophoresis (dysproteinemias such as multiple mieloma), Urea, electrolytes and creatinine (renal disease in association with hypertension), Thyroid function tests (associated with dyslipidemia), ECG (left ventricular hypertrophy secondary to hypertension).

Treatment

No known effective medical treatment is available for either the prevention of or the treatment of central retinal vein occlusion (CRVO). Identifying and treating any systemic medical problems to reduce further complications is important.

Advocated treatments are as follows:

Aspirin
Anti-inflammatory agents
Isovolemic hemodilution
Plasmapheresis
Systemic anticoagulation with warfarin, heparin, and alteplase
Fibrinolytic agents
Systemic corticosteroids
Local anticoagulation with intravitreal injection of alteplase
Intravitreal injection of ranibizumab
Intravitreal injection of aflibercept
Intravitreal injection of triamcinolone
Intravitreal injection of bevacizumab
Dexamethasone intravitreal implant

Case report 1

B.M is a 64 year old man who presented at eye clinic, UHC"Mother Theresa" Tirana, 3 days after having blurred vision on his left eye. He had a history of hypertension for 8 years. After the examination it was noted a CRVO with severe macular edema on left eye with BCVA 2/20. (figure nr. 3)

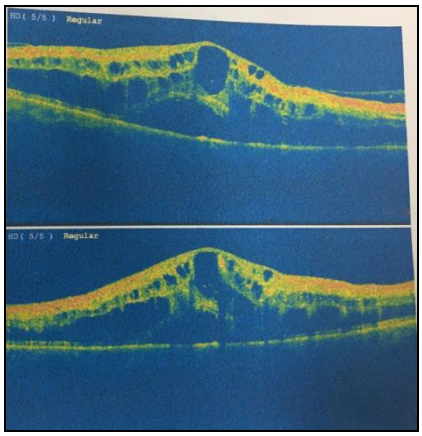

Figure 3.

Immediately after the examination and full laboratory tests, we performed an 0.05ml intraviteal injection of aflibercept 40mg/ml (EYLEA), followed by 2 more injection for the next 2 months. During this period we advised him to use timolol maleate 0.5% drops and acetazolamide tab 250mg/p.os. After 3 months we noticed a reduction of macular edema and a BCVA 8/20 (figure nr. 4).

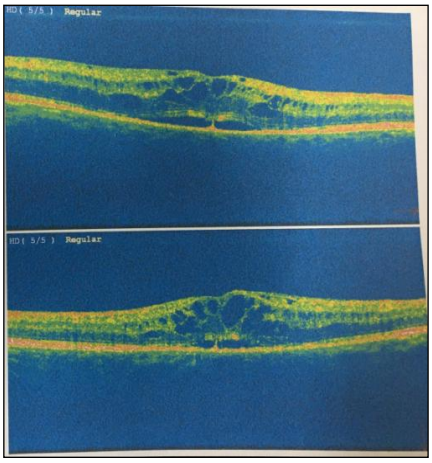

Figure 4.

Case report 2

Sh.V is a 58 years old woman with a 10 years history of Diabet Mellitus and hypertension. She presented at the eye clinic 2 weeks after she noticed a reduction on her visus on the left eye. After the examination with OCT and fluorescein angiography we noticed a ischemic CRVO with severe macular edema and VA 1/20, and immediately performed a intravitreal injection of aflibercept 40mg/ml. (figure nr. 5). This injection was followed by 3 other injections every 4 weeks.

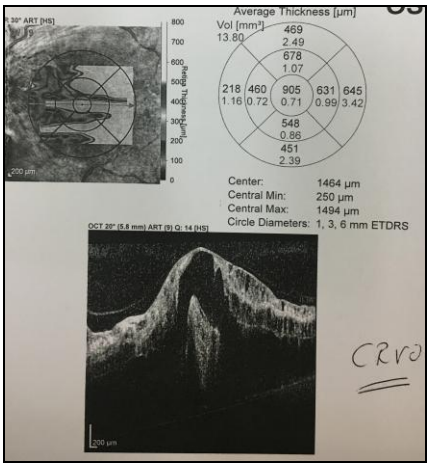

Figure 5.

After 5 months we noticed a reduction of macular edema from 905 µm to 525 µm on OCT and an improvement on patient visual acuity at about 4/20. (figure nr. 6)

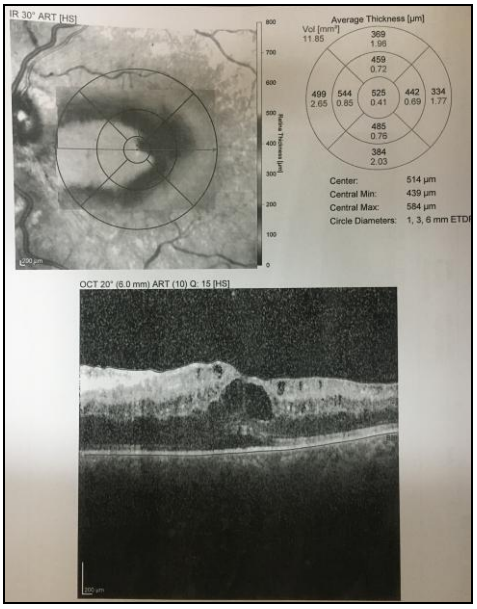

Figure 6.

Case report 3

B.B is a 51 year old man with history of hypercholesterolemia and hypertension. He presented at our clinic with a blurred vision on his right eye since the night before. After the examination it was noted an ischemic CRVO with a severe macular edema at about 880 µm. We performed an intravitreal injection of aflibervept 40mg/ml wich was followed by 4 other injection in the next 6 months. In figure nr 7 we can notice the diference on macular edema after 5 injection of aflibercept. Huge reduction of macular edema was noticed and the patient gained a visus from 2/20 to 10/20.

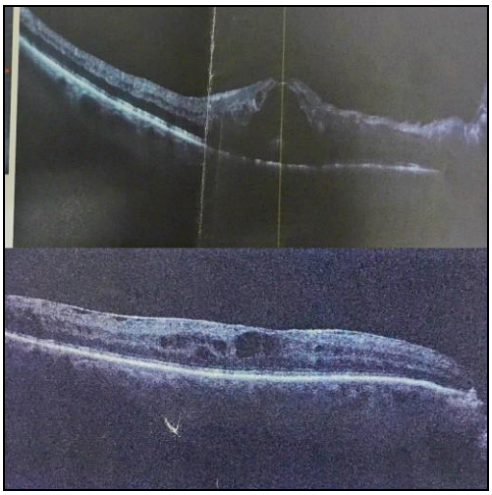

Figure 7.

Discussion

The increase in VEGF, is triggered by hypoxia in pathological conditions. Increased plasma levels of VEGF were first found in diabetic patients, and were highest in preproliferative and proliferative retinopathy. Human eyes with CRVO showed evidence of intraretinal upregulated expression of VEGF mRNA. Indeed, raised levels of VEGF have been reported in both the aqueous and vitreous fluid of patients with ischemic CRVO, and are responsible for the increase in vascular permeability that leads to macular edema. Aqueous and vitreous levels of VEGF were significantly correlated with the severity of ME. Delivering anti-VEGF antibody into the eye therefore, in theory, should help in the treatment of CRVO-ME, as has been shown in diabetic ME. Intravitreal aflibercept injections have resulted in a substantial decrease in VEGF under physiologic levels and have remained low with the loading doses of three consecutive monthly retreatments.

The Ophthalmic Technology Assessment Committee Retina/Vitreous panel of the American Academy of Ophthalmology evaluated available literature regarding efficacy of available pharmacotherapies in the treatment of macular edema due to CRVO. The panel reported that intravitreal anti-VEGF therapy is safe and effective over 2 years for macular edema and that delayed treatment is associated with worse visual outcomes.

Two parallel trials, the COPERNICUS and GALILEO studies, evaluated the efficacy and safety of intravitreal aflibercept injection for the treatment of macular edema secondary to CRVO. Aflibercept injection demonstrated a statistically significant difference in the proportion of patients who gained 15 or more letters from baseline at week 24 compared with placebo in each study. The visual and anatomic improvements were diminished after continued PRN dosing, with a reduced monitoring frequency from weeks 52 to 100.

Conclusion

The exact pathogenesis of the CRVO is not known, and various medical modalities of treatment have been advocated by multiple authors with varying success in preventing complications and in preserving vision. So no known effective medical treatment is available for either the prevention of or the treatment of central retinal vein occlusion (CRVO). Anyway macular edema is a treatable cause of decreased visual acuity in patients with CRVO. Various treatment modalities have been used, with significant progress in stabilizing or improving visual acuity. One of the best and safest way to do that is by using intravitreal anti-VEGF. We advice to perform 3 intravitreal injection of anti-VEGF every month, followed by injection every 2 month after that, depending on the macular edema of each case.

The studies and experience demonstrate that long-term anti-VEGF therapy and more frequent monitoring is necessary to control macular edema in many patients with CRVO, likely because the continued ischemia leads to continued VEGF production.

References

A. Pielen, N. Feltgen, C. Isserstedt, J. Callizo, B. Junker, and C. Schmucker, "Efficacy and safety of intravitreal therapy in macular edema due to branch and central retinal vein occlusion: a systematic review," PloS One, vol. 8, no. 10, article e78538, 2013.

T. Braithwaite, A. A. Nanji, K. Lindsley, and P. B. Greenberg, "Anti-vascular endothelial growth factor for macular oedema secondary to central retinal vein occlusion," Cochrane Database of Systematic Reviews, no. 5, article CD007325, 2014.

A. R. Berger, A. F. Cruess, F. Altomare et al., "Optimal treatment of retinal vein occlusion: Canadian expert consensus," Ophthalmologica Journal International Ophtalmologie International Journal Ophthalmology Zeitschrift Für Augenheilkunde, vol. 234, pp. 6–25, 2015.

P. A. Campochiaro, J. S. Heier, L. Feiner et al., "Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a phase III study," Ophthalmology, vol. 117, pp. 1102.e1–1112.e1, 2010.

F. G. Holz, J. Roider, Y. Ogura et al., "VEGF trap-eye for macular oedema secondary to central retinal vein occlusion: 6-month results of the phase III GALILEO study," The British Journal of Ophthalmology, vol. 97, pp. 278–284, 2013.

J. F. Korobelnik, F. G. Holz, J. Roider et al., "Intravitreal aflibercept injection for macular edema resulting from central retinal vein occlusion: one-year results of the phase 3 GALILEO study," Ophthalmology, vol. 121, pp. 202–208, 2014.

Y. Ogura, J. Roider, J. F. Korobelnik et al., "Intravitreal aflibercept for macular edema secondary to central retinal vein occlusion: 18-month results of the phase 3 GALILEO study," American Journal of Ophthalmology, vol. 158, no. 5, pp. 1032–1038, 2014.

D. Boyer, J. Heier, D. M. Brown et al., "Vascular endothelial growth factor trap-eye for macular edema secondary to central retinal vein occlusion: six-month results of the phase 3 COPERNICUS study," Ophthalmology, vol. 119, pp. 1024–1032, 2012.

D. M. Brown, J. S. Heier, W. L. Clark et al., "Intravitreal aflibercept injection for macular edema secondary to central retinal vein occlusion: 1-year results from the phase 3 COPERNICUS study," American Journal of Ophthalmology, vol. 155, pp. 429.e7–437.e7, 2013.

Germany Ophthalmology Society and Retina Society, "Professional Asociation of German Ophthalmologists. [statement of the German Ophthalmology Society, the Retina Society and the Professional Association of German Ophthalmologists for the treatment of macular edema in retinal vein occlusion: therapeutic strategies]," Ophthalmol Zeitschrift der Deutschen Ophthalmologischen Gesellschaft, vol. 109, pp. 818–831, 2012.

A. Bajor, A. Pielen, and L. Danzmann, "Retinal vein occlusion-which treatment when?" Klinische Monatsblätter für Augenheilkunde, 2017.

N. Feltgen and A. Pielen, "Retinal vein occlusion: therapy of retinal vein occlusion," Ophthalmology Zeitchrift Deutschen Ophthalmologischen Gesellschaft, vol. 112, pp. 695–704, 2015.

G. Coscas, A. Loewenstein, A. Augustin et al., "Management of retinal vein occlusion—consensus document," Ophthalmologica Journal International Ophtalmologie International Journal Ophthalmology Zeitschrift Für Augenheilkunde, vol. 226, pp. 4–28, 2011.

J. S. Pulido, C. J. Flaxel, R. A. Adelman, L. Hyman, J. C. Folk, and T. W. Olsen, "Retinal vein occlusions preferred practice pattern(®) guidelines," Ophthalmology, vol. 123, pp. 182–208, 2016.

C. Chiquet, A. M. Bron, M. Straub et al., "Retinal vein occlusions: therapeutic switch in macular oedema treatment with a 12-month follow-up," Ophthalmic Research, vol. 55, pp. 152–158, 2016.

"Study of comparative treatments for retinal vein occlusion 2 (SCORE2) October 2016 https://clinicaltrials.gov/ct2/show/NCT01969708?term=aflibercept+retinal+vein+occlusion&rank=3.